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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/520,130	03/07/2000	Robert Arathoon	P1099R2	1353

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EXAMINER
HUNT, JENNIFER ELIZABETH

ART UNIT	PAPER NUMBER
1642	8

DATE MAILED: 02/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/520,130	ARATHOON ET AL.	
	Examiner	Art Unit	
	Jennifer E Hunt	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14,16-18,31 and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *12-14,16-18,31 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____

[illegible]

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). [illegible]
4. ☐ [illegible]
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Other: [illegible]

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group IV, claims 12-14, 16-18, 31 and 33, and further of the species "IgG" and anti-Ob-R/anti Her3", in Paper No. 6 is acknowledged. The traversal is on the ground(s) that there is no undue search burden because the groups are classified in the came class and subclass This is not found persuasive because as set forth in the original restriction requirement, the Groups are drawn to patentably distinct molecules and require different non-coextensive searches of both patent and non-patent literature.

The requirement is still deemed proper and is therefore made FINAL.

2. Acknowledgement is made of applicant's cancellation of claims 1-11, 15, 19-30, and 32, and addition of new claims 34-38. Claims 12-14, 16-18, 31, and 33-38 are pending and considered herein.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of protuberance and cavity cannot be determined. It is not clear what would be considered a protuberance and cavity and what would not.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 12-14, 16-18, 31, and 33-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the bispecific antibody anti-Ob-R/anti-HER3 where the variable region of both light chains is identical, does not reasonably provide enablement for any multispecific antibody which contains variable light chains which are 80% or 90% or 95% or 98% or 99% similar to each other, including non-cognate heavy and light chain combinations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the art, 5) the predictability or the unpredictability of the art, and 6) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims broadly encompass any multispecific antibody which by coincidence or by design, has light chain molecules which are at least 80% or 90% or 95% or 98% or 99% similar to each other. The antibody can be bispecific, trispecific, and so forth. Further, the arms can bind to literally any antigen, provided only that they each bind to different antigens. Further, as the claims are broadly recited, the heavy and light chain may be non-cognate.

The specification discloses a very specific method of screening light chain phage libraries, identifying antibodies which bind to different antigens, but have identical light chains, and selecting those to combine in production of a bispecific antibody, for the purpose of increase yield of functional bispecific antibodies from a quadroma.

With regard to the breadth of the claims, the claims encompass literally any bi-, tri-, or other multispecific antibody, provided only that the arms of the antibody bind to distinct antigens, but that their light chains are at least 80% identical. There are numerous types of multispecific antibodies (bispecific, trispecific, and so forth). Searching for distinct antigen specificity with coincidental light chain identity becomes an exponentially difficult task as the number of distinct binding arms increases. While the two antigen specificities exemplified by the instant specification

improbable as the number of distinct antigens bound increases. Production of bispecific antibodies is already a complex art. The additional sets of determining

light chain identity only further complicates the difficulties with isolating and producing an effective antibody.

Further with regard to the breadth of the claims, the combination of possible antigens is limitless, and it is not clear that more than the two exemplified antigens exhibit light chain identity as is required by the instant claims. Further, unspecified method of light chain screening and antibody production instantly claimed is far broader than the method of phage library screening and quadroma production which is exemplified in the specification.

With regard to predictability of production of a multispecific antibody by the instant method, it is known in the art that production of an effective bi- or multispecific antibody can be complex. The task requires selection of monoclonals which effectively bind their antigen, and which still function effectively when combined in the different conformation of a bi- or tri-specific antibody. Songsivilai et al., Clin. Exp Immunol., Vol. 79, pages 315-321, 1990 discusses some of the difficulties with producing bispecific antibodies, including the difficulty of fusing hybrids, the instability of the resulting cell lines, the low yield, and difficulty in purification, the effect of chemical modifications on antigen binding function (see pages 116-318).

Further, it is noted that the claims do not require that the light chain is the

encompass antibodies which would have a light chain which was only 80% or 90% or 95% or 98% or 99% similar to it's natural light chain. It is well known that amino acid

changes in antibodies can have a drastic effect on antibody conformation and function. Thus production of bi- or multispecific antibodies, and/or alteration of the corresponding light chain to a heavy chain would often produce a non-functional antibody. The formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen binding function.

chains is insufficient support under the first paragraph of 35 U.S.C 112 for claims which encompass any and all multispecific antibodies having 80% or greater similarit

between their light chains including those yet undiscovered. The courts have held that:

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based In some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence, not In compliance with the first paragraph of U.S.C. 112; that paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill In the art; In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement In the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; In cases involving unpredictable factors, such as chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. "In re Fisher 427 F.2d 833, 166 USPQ 18 (CCPA 1970)

Therefore due to the lack of guidance in the specification, the lack of working examples, the breadth of the claims and the nature of the invention, and the state of

be enabled to make and use the invention commensurate in scope with the claims.

7. Claims 12-14, 16-18, 31, and 33-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one of skill in the art can reasonable conclude that applicant had possession of the claimed invention at the time of filing. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111 clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for the purpose of the 'written description' inquiry, whatever is now claimed." The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is instantly claimed."

Applicant is reminded that *Vas-Cath* makes clear the written description provision of 35 U.S.C. is severable from it's enablement provision.

The specification discloses a very specific method of screening light chain phage libraries, identifying antibodies which bind to different antigens, but have

quadroma. The specification discloses only two bispecific antibodies which are produced in this manner.

The claims encompass any multispecific antibody which by coincidence or by design, has light chain molecules which are at least 80% or 90% or 95% or 98% or 99% similar to each other. The antibody can be bispecific, trispecific, and so forth. Further, the arms can bind to literally any antigen, provided only that they each bind to different antigens. Further, as the claims are broadly recited, the heavy and light chain may be non-cognate.

Thus while the production of additional bispecific or multispecific antibodies is contemplated, and further the production of antibodies with similar but non-identical light chains is contemplated, the instant specification does not disclose the structure of the antibodies, absent that their light chains have 80% or greater identity, nor does it provide a written description of any other identifying physical or function characteristics correlative with claimed antibodies in sufficient detail to lead to the conclusion that applicant had possession of the claimed invention. Only two bispecific antibodies, having identical light chains are produced. No multispecific antibodies, or antibodies with non-identical light chains are produced. Thus the claims encompass a broad genus of molecules, which the specification discloses only two. See *Amgen Inc. V. Chugai Pharmaceutical Co.*, 927 F.2d. 1200, 18 USPQ2d 1601 (Fed. Cir. 1991); *Fiers v. Revel*, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir., 1993); and *University of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997)

other identifying characteristics of the claimed invention by the instant specification. It is concluded that the specification did not contain a written description of the

invention in such full, clear, concise and exact terms or in sufficient detail that one skilled in the art can reasonable conclude that applicant had possession of the claimed invention at the time of filing.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E Hunt whose telephone number is (703) 308-7548. The examiner can normally be reached on Monday-Friday, 6-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

Jennifer E Hunt
Examiner

jeh
February 11, 2002